CYCLOSPORIN-CONTAINING POWDER COMPOSITION

TECHNICAL FIELD

The present invention relates to a cyclosporin-containing powder composition. More particularly, the present invention relates to a cyclosporin-containing powder composition having an improved stability and an increased bioavailability, which contains cyclosporin, a non-ionic hydrophilic surfactant and a porous carrier. In addition, the present invention relates to a process for preparing the cyclosporin-containing powder composition.

BACKGROUND ART

Cyclosporin is a peptide compound having a unique structure consisting of 11 poly-N-methylated amino acids and has been known as having useful pharmacological activities, particularly immunosuppressive activity, antiinflammatory activity and the like. Cyclosporin compound which was first isolated from the natural product is ciclosporin as a spontaneous fungi metabolite, which is generally known as cyclosporin A and is the most widely used cyclosporin compound at the present time. Since cyclosporin A is first discovered, numerous cyclosporin compounds present in the natural world have been isolated and identified. At the present time they are prepared in industrial scale by a synthetic or semi-synthetic method or by a modified culture method.

Cyclosporin A has been recognized as having a very great value as an immunosuppressive agent in the clinical field. The effectiveness of cyclosporin A as the immuno-suppressive agent is demonstrated particularly in the field of organ transplantation, for example, transplantation of heart, lung, liver, kidney, pancreas, bone marrow, skin and cornea tissues. In addition, cyclosporin A is very useful for the treatment of autoimmune diseases and inflammatory conditions, particularly arthritis, for example, rheumatoid arthritis, chronic arthritis, progressive arthritis and arthritic malformation, and inflammatory conditions caused by autoimmune components such as rheumatic diseases.

However, in spite of the great effectiveness of cyclosporin in the field of organ transplantation and treatment of autoimmune diseases the clinical use of cyclosporin is very restricted because cyclosporin is very difficult to provide an effective and convenient administration method and has undesirable side effects such as serious nephrotoxicity. In addition, since cyclosporin is highly hydrophobic, it cannot be expected that the formulation prepared by a conventional method will provide an effective therapeutic effect.

In order to solve the above-mentioned problems related to cyclosporin U.S. Pat. No. 4,388,307 suggests a method for preparing a liquid formulation for internal use by mixing cyclosporin with Labrafil or Miglyol, ethanol and corn oil. However, such a liquid formulation should be administered as a dilution in potable water and is very difficult to provide the desired precise dosage for oral administration. Such problems involved in the liquid formulation could be solved by using a soft gelatin capsule formulation.

However, the cyclosporin soft gelatin capsule preparation has also a problem that ethanol as a solvent for cyclosporin should be used in a large amount in order to keep cyclosporin in the state of solution. Specifically, when ethanol, which has a low boiling point, is evaporated from the capsule preparation, cyclosporin is precipitated and the precipitated cyclosporin is substantially not absorbed in the living body. Accordingly, the reduced ethanol content due to evaporation during storage has a significant influence upon the effect of cyclosporin preparation. In order to avoid such problem the soft gelatin capsule should be packed in the closed space, or wrapped in a special packing material such as a sealing film foam package or an aluminum film foam package, to minimize the evaporation of ethanol from the soft capsule preparations. However, such special package contributes to the increase in the product volume and the production costs. Further, it has been reported that the stability of the soft capsule preparation wrapped in such special package reduces as the storage period is getting longer.

For example, Sandimun^R which is presently commercially available in the form of a liquid preparation for internal use, an injectable preparation and a soft capsule preparation has also the above-mentioned problems. Specifically, the Sandimun liquid preparation has the disadvantages that it should be diluted with milk or juice before administration and thus is difficult to provide a precise dosage. The soft capsule preparation has also a problem in that when the ethanol content in soft capsules is varied, cyclosporin dissolved in ethanol is precipitated out to decrease the bioavailability thereof. In order to avoid such problem Sandimun preparation should be wrapped in a special packing material which results in the increase of the product volume and the production costs.

In order to solve the above-mentioned disadvantages of the prior art British Patent Publication No. 2222770A proposes a preparation containing cyclosporin as an active ingredient and particularly in the form of a microemulsion or a microemulsion preconcentrate. The composition of this patent includes (1) a hydrophilic phase, (2) a hydrophobic phase and (3) a surfactant. In this patent, a method of formulating the composition into a hard gelatin capsule preparation is also described. However, since the composition to be filled in the hard gelatin capsule is in the liquid form, the capsule should be sealed by using a special technique, i.e. Quali-seal technique.

In addition, Korean Laid-open Patent Publication No. 90-12625 discloses a cyclosporin galenic preparation comprising cyclosporin as an active ingredient, a fatty acid sugar monoester, and a diluent or a carrier. However, since the composition of this preparation is also in the liquid state such as solution or suspension, the hard gelatin capsule filled with the composition should be sealed by means of Quali-seal technique as in British Patent Publication No 2222770. In addition, when the composition is absorbed into a carrier to prepare the tablet formulation, it has also a disadvantage that the stability of tablet preparations is bad due to a high hygroscopic property of saccharose monolaurate L-1695 as the fatty acid sugar monoester [see Pharmaceutical Research, Vol. 6, No. 11, 1989, p958, "Solid Surfactant Solutions of Active Ingredients in Sugar Esters" and International Journal of Pharmaceutics, Vol. 92, 1993, p197, "Applications of sucrose laurate, a new pharmaceutical excipient, in peroral formulations of cyclosporin A"]. According to the above-mentioned papers, the fatty acid sugar monoester such as saccharose monolaurate L-1695 has a hygroscopic property, it should be treated under the drying condition. Thus, under the condition of 70% relative humidity the dry fine powder should be subjected to the subsequent procedure within 30 minutes after its preparation. Further, the fatty acid sugar monoester is unsuitable for the preparation of any formulation by a direct compression, due to its poor fluidity. For improving the high hygroscopic property of saccharose monolaurate this patent uses an additive such